

# Effect of Phenytoin in Wound Healing: A Review

Nivaasini Sivarajah

Saveetha Dental College and Hospitals, Chennai, India  
Corresponding Author Email ID: nivaasini92[at]gmail.com

**Abstract:** Phenytoin (diphenhydantoin or Dilantin) is a highly effective and widely prescribed anticonvulsant agent and antiarrhythmic agent in the treatment of grand mal and psychomotor epilepsy. Phenytoin was introduced into therapy in 1937 for effective convulsive disorder with a common side effect being gingival hyperplasia. In dermatology due to the stimulatory effect on the connective tissue it is used in wound healing treatment such as diabetic ulcer which affects almost 15% of diabetic individuals, Decubitus ulcer or also known as bed sore or pressure ulcer, chronic leg ulcer and epidermolysis simplex bullosa. The mechanism of action of phenytoin is it increases gene express of the platelet-derived growth factor B chain in macrophages and monocytes. Healthy granulation tissue appears earlier. Common side effects of phenytoin which occurs due to long term use are Gingival Hyperplasia, Coarsening of the facies, Enlargement of the lips and thickening of the scalp and face.

**Keyword:** Phenytoin, wound healing, diabetic ulcer, periodontitis

## 1. Introduction

Phenytoin is a highly effective and widely prescribed anticonvulsant agent and antiarrhythmic agent in the treatment of grand mal and psychomotor epilepsy<sup>3</sup>. In dermatology the effect of phenytoin on the connective tissue suggested possibility for its use in wound healing<sup>5</sup>. Studies have shown that topical phenytoin to promote healing of diabetic ulcer, venous stasis ulcer, decubitus ulcer, traumatic wounds, burns and leprosy trophic ulcer<sup>1</sup>. Phenytoin may have the potential to alter the dynamics of wound healing; suggesting a therapeutic use for the stimulation of chronic wounds<sup>2</sup>. Phenytoin may promote wound healing by a number of mechanisms, including stimulation of fibroblast proliferation, facilitation of collagen deposition, glucocorticoids antagonism and antibacterial activity<sup>4</sup>.

## 2. Mechanism of Action of Phenytoin

Phenytoin increases gene express of the platelet-derived growth factor B chain in macrophages and monocytes. Healthy granulation tissue appears earlier<sup>4</sup>. Phenytoin increases proliferation of fibroblast b 50-90 % in two fibroblast cell line, but does not affect the heart, lung, kidney and squamous epithelium<sup>1</sup>. Topical phenytoin also eliminates *Staphylococcus aureus*, *E. coli*, *Klebsiella* and *Pseudomonas* from wounds within 7-9 days. It more readily clears all the gram negative bacteria compared to gram positive bacteria<sup>2</sup>.

## 3. Phenytoin in Wound Healing

### Diabetic Ulcer:

Diabetic foot ulcer is common and estimated to affect 15% of all diabetic individuals. Management of diabetic foot ulcer requires a multisystem approach<sup>11</sup>. Diabetic foot ulcer precede to almost 85% of amputation<sup>12</sup>. A study was conducted on 80 patients with diabetic ulcer by the Department of surgery of El-Minia faculty of medicine. Topical phenytoin was used on 40 patients and conservative methods were used on 40 other patients. Patients who were treated with topical phenytoin ulcer

healed faster and there was no reoccurrence of ulcer within 30 months of follow up<sup>4</sup>. In another study conducted by the Patil medical college on 100 patients. Patients were divided into 2 groups, one group underwent saline treatment for diabetic ulcer and the other group underwent phenytoin treatment. The group which was given phenytoin treatment ulcer shrunk and healed faster compared to the group which was given saline treatment<sup>11</sup>. Estimated healing time for a diabetic ulcer treated by phenytoin is 21 days compared to ulcers treated with saline which takes estimated time of 45 days<sup>1</sup>.

### Decubitus Ulcer:

Decubitus ulcer is also known as bedsore or pressure ulcers. This sores usually occurs on the skin covering the bone and usually occurs in area where more pressure is applied<sup>13</sup>. Zayat conducted a study on phenytoin compared to chlorhexidine in fifteen patients. In the phenytoin healing group the healing time only took time from 1-3 weeks while the other group took time from 6-8 weeks<sup>1</sup>. A study which was conducted by the El-Minia medical university proved that patients treated with phenytoin had faster healing time compared to the other treatment given<sup>4</sup>.

### Chronic Leg Ulcer:

Chronic leg ulcer have different aetiologies such as animal bites, post-operative wounds and burn injury, topical ulcer, varicose vein and etc<sup>14</sup>. There is no specific regime treatment for chronic leg ulcer<sup>9</sup>. Syatemic and topical antibiotics has been used to control infection, loacal antiseptic with numerous chemical has been used but have been limited due to poor nutritional status and vascular insufficiency<sup>11</sup>. Edinburgh University proved that phenytoin is a better healing agent compared to slaked lime<sup>14</sup>.

### Epidermolysis Bullosa

Epidermolysis bullosa is one of a group of genetic conditions called epidermolysis bullosa that cause the skin to be very fragile and to blister easily. Blisters and areas of skin loss occur in response to minor injury or friction, such as rubbing or scratching<sup>8</sup>. In epidermolysis bullosa,

levels of collagenase are increased<sup>2</sup>. Phentoin helps to inhibit collagenase in vitro. By inhibiting the collagenase activity, phenytoin has been proved to stabilize collagen fibrils and decrease the blister formation<sup>15</sup>. Phenytoin reduces the contraction of recessive dystrophic epidermolysis bullosa fibroblast populated collagen gels<sup>2</sup>.

#### Side Effects of Phenytoin

Common side effects of phenytoin which occurs due to long term use are Gingival Hyperplasia, Coarsening of the facies, Enlargement of the lips and thickening of the scalp and face<sup>2</sup>. Phenytoin can also cause hirsutism in about 12% of children who are receiving phenytoin, This usually occurs within 3 months of initiating the therapy, It usually occurs in the trunk and the face<sup>4</sup>. Other common side effects which can be caused by phenytoin are collagen Vascular side effects, generalised cutaneous eruptions, hypersensitivity syndrome, pseudolymphoma and birth defects<sup>2</sup>. Some patients who are treated with phenytoin have a transient burning sensation, rash which develops due to phenytoin and hypertrophic granulation tissue<sup>5</sup>.

#### 4. Conclusion

After 60 years of use, phenytoin uses and mechanisms continue to be defined. The inhibition of collagenase by phenytoin gives it a real role in facilitating the healing of ulcers. Phenytoin also has complex effects on the immune system, in particular an induction of a Th2-type response, which might underlie its common induction of eruptions and immunologic effects. It can also be seen as an antagonist of cortisol and this might buttress its effects on wound healing and immune dysregulation. It is used in hard-to-treat conditions that involve excessive or dysfunctional production of collagen, such as morphea and epidermolysis bullosa. Topical Phenytoin decreases bacterial load, forms healthy granulation tissue and helps in better graft take up than the conventional dressing<sup>5</sup>. Proposed action of phenytoin includes accelerated fibroblast proliferation, formation of granulation tissue and deposition of connective tissue components and bacterial contamination of the ulcer helps in the healing of ulcer faster than conventional method<sup>7</sup>. Phenytoin and related drugs remain promising therapies and fertile fields for future investigation.

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